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EDITORIAL

Arteriovenous malformations of the brain: ready to randomise?

R Al-Shahi, C Warlow

When arteriovenous malformations (AVMs) of the brain were first described in the middle of the 19th century, deciding on treatment was easy, because there was none. Since the first reports of the neurosurgical exposure of brain AVMs at the end of that century,^{1,2} their management has been dogged by controversy. In 1928, Cushing and Bailey wrote, "...to extirpate one of these aneurysmal angiomas in its active state would be unthinkable...";³ but, while their book was in press, Walter Dandy published a case series of people whose brain AVMs had been surgically resected (with variable success).⁴ Later developments in catheter angiography, bipolar coagulation, the operating microscope, and stereotactic surgery have all encouraged surgical intervention and no doubt improved the completeness and safety of resection.^{5,6} However, clinicians still struggle with the original dilemma of whether some brain AVMs should be treated at all.

Interventions for brain AVMs diversified during the latter half of the 20th century, giving clinicians a further dilemma about which intervention to use should treatment be appropriate. Endovascular embolisation, by injecting artificial agents in the afferent feeding vessels of brain AVMs, was first reported in 1960.⁷ The technique has been refined ever since, initially as an adjunct to neurosurgical excision,⁸ but more recently, with the development of microcatheters and liquid polymer glues, as a potentially curative procedure.⁹ Unfractionated stereotactic radiotherapy, confusingly referred to as "radiosurgery" by some, was first used to treat brain AVMs a decade after the first report of endovascular embolisation.¹⁰ Stereotactic radiotherapy, using gamma knife, linear accelerator, and charged particle (proton beam) techniques, can provoke vascular obliteration of compact brain AVMs ≤ 3 cm in diameter and of larger AVMs that have been reduced to this size with embolisation. Despite the chronology of the development of these interventions, there are far more large published

studies of stereotactic radiotherapy than of embolisation and surgery put together.

SHORTAGE OF EVIDENCE

So, how good is the evidence for the beneficial and adverse effects of these treatments?¹¹ What is the balance between them? Which brain AVMs should be treated, and with what? A single randomised controlled trial (RCT) found no major differences between n-butyl-cyanoacrylate (n-BCA) liquid and polyvinyl alcohol particles in the pre-operative embolisation of brain AVMs.¹² A similar RCT of Onyx (a new non-adhesive liquid embolic material) versus n-BCA in the pre-operative embolisation of brain AVMs has been completed but not published (G Duckwiler, UCLA Medical Center, personal communication). Both of these RCTs were funded by industry, they did not appear to be powered to test equivalence of the interventions, and were conducted to obtain USA Food and Drug Administration approval for the embolic agents. Otherwise, there are no RCTs whatsoever.

The remainder of the vast literature about the benefits and risks of treating brain AVMs is composed of case series without even a concurrent control group.¹¹ These studies have frequently been retrospective and participants were amassed over long periods of time, during which technical developments in treatment occurred. Moreover, the people in these case series were usually selected for a particular intervention, or rejected from the other interventions available, on the basis of the vascular anatomy ("angioarchitecture") of the brain AVM.¹³ Therefore, the inevitable heterogeneity of angioarchitecture between these series makes their comparison with each other difficult, if not impossible. Even the description of the effects of a single modality of treatment in these series has been complicated by the inclusion of people who had already received one or more of the other interventions. Most of these studies have not used standard, independently assessed measures of morbidity, disability or

dependence. Rather, by using the occurrence of haemorrhage during follow up as the main outcome instead, these studies may have completely missed disability from other causes (such as radiation induced damage¹⁴), or conversely, overestimated morbidity because haemorrhage from a brain AVM may only be disabling for the minority of people.¹⁵ Without a control group, it has been difficult to reliably ascertain whether any change in haemorrhage rate after treatment is an improvement on conservative management.¹⁴ Moreover, the popular comparison of haemorrhage rates before and after intervention¹⁴ may simply reflect the waning of the haemorrhage rate after a bleed at initial presentation,^{16,17} often obscured because treatment outcomes have not been stratified by initial presentation. Another unsatisfactory primary outcome after treatment, extensively used in studies of stereotactic radiotherapy,¹⁸ has been brain AVM "obliteration" (lack of visualisation on angiography); this tells us nothing about disability, and brain AVMs have been reported to recanalise after apparent obliteration, especially in the rare studies where follow up has been sufficiently long to capture such outcomes.

GENERALISATIONS ABOUT THE EFFECTS OF TREATMENT

Criticisms of the literature aside, we can make some tentative generalisations:

- Cure (judged by apparent obliteration on angiography) has been least common among people selected for embolisation, greater for those selected for stereotactic radiotherapy, and greater still for those selected for surgery.
- A review of the effects of surgical excision since the 1970s found overall post-operative case fatality to be ~3% and permanent "morbidity" to affect ~9%.¹⁹ These findings are comparable to the Columbia AVM study group cohort where ~6% of people were judged (independently, by a neurologist) to have a disabling neurological deficit 1 year after surgery.⁶
- These surgical studies broadly confirmed that the main components of the 5 point Spetzler-Martin grading system (table 1) predict postoperative outcome, which is generally very good for grade I to III brain AVMs.²⁰
- For endovascular embolisation alone, ~10 months after treatment, case fatality was 1%, and 13% of people in the Columbia AVM study group cohort were judged (independently, by a neurologist) to have new

neurological deficits (which were not predicted by the Spetzler-Martin grading system, but rather by increasing age and increasing number of embolisations).²¹

- For stereotactic radiotherapy alone, ~34 months after treatment, case fatality was 0.2%, and radiation injury affected ~6% (which was disabling for ~2% of the whole group).²²
- While minimum radiation dose and AVM size predict the probability of obliteration, complications vary by brain location and, to a lesser extent, AVM volume.²³

INDIRECT COMPARISON OF TREATMENT EFFECTS WITH UNTREATED CLINICAL COURSE IS UNSATISFACTORY

Unfortunately, clinicians have to make a treatment decision, based on an indirect comparison of these "average" treatment outcomes with the "average" untreated clinical course for people with a brain AVM. Data on specific predictors of outcome for any individual person are limited. Furthermore, the few cohorts that provide reliable data about untreated clinical course have usually consisted of brain AVMs that were impossible or unsuitable to treat, outcome has seldom been segregated according to mode of presentation, follow up has been short, and methods of analysis have differed.²⁴ Even the two most recent studies of whether initial presentation with haemorrhage confers a worse prognosis for subsequent haemorrhage do not concur.^{16, 25} It is, however, likely that initial presentation with intracranial haemorrhage and deep venous drainage do confer a higher risk of subsequent haemorrhage for untreated brain AVMs,^{16, 17} at least in the first few years after presentation.

Spetzler-Martin grading scale²⁰

Characteristic	Score
Size of AVM	
Small (<3 cm)	1
Medium (3–6 cm)	2
Large (>6 cm)	3
Eloquence of adjacent brain*	
Not eloquent	0
Eloquent	1
Pattern of venous drainage†	
Superficial only	0
Deep	1

Grade = total of scores. *Eloquent: sensorimotor, language and visual cortex; hypothalamus and thalamus; internal capsule; brainstem; cerebellar peduncles; and deep cerebellar nuclei. †Superficial: cortical venous system and cerebellar hemispheric veins (that drain directly into the straight or transverse sinuses).

The well recognised heterogeneity in prognosis for haemorrhage among brain AVMs is starting to be understood, and this probably invalidates popular formulae that estimate someone's lifetime risk of haemorrhage based on the incorrect assumption that the annual risk of haemorrhage is constant.²⁶

Brain AVMs now pose a regular management problem because our ignorance of their true clinical course has been overshadowed by the interest in and pace of development of surgical, endovascular, and radiation interventions, the seemingly favourable short term effects of these treatments for most people, and their widening availability. However, these treatments are costly, especially for people whose brain AVMs are more difficult to treat and who have worse outcomes,²⁷ and there is likely to be variation between specialist centres and different countries in which treatments are used, according to local opinion, expertise, and treatment availability.

Not surprisingly, therefore, there is still disagreement about whether to treat people with brain AVMs at all, and if so, which intervention(s) to use.

TO TREAT OR NOT

Ideally, any treatment decision should be taken by a multidisciplinary team composed of a neurologist, neurosurgeon, radiotherapist, and neuroradiologist. Whether to treat a brain AVM now seems fairly straightforward if it has been detected following an intracranial haemorrhage; the early risk of re-bleeding makes intervention justified for all but those AVMs that are impossible to treat and those people who are so disabled, so elderly, or so burdened with other comorbidities that "conservative management" is desirable because treatment would not be beneficial. More than half of brain AVMs come to medical attention with problems other than intracranial haemorrhage,²⁸ and informing these people's choices about treatment is difficult because of the inadequacies of the available data. A landmark, albeit post hoc, analysis of the Columbia AVM cohort, so far only published as an abstract, suggests that the interventional treatment of unruptured brain AVMs is actually more likely to result in subsequent haemorrhage and/or disability than conservative management over ~5 years follow up.²⁹ This observation has reinforced the proposal for a much needed RCT (ARUBA), which will compare interventional treatment of unruptured brain AVMs with their conservative management. Potential collaborators are encouraged to visit the ARUBA study website

(<http://www.arubastudy.org>) to register their interest.

TO TREAT WITH WHAT

Once a decision to intervene has been made, clinicians are faced with the final dilemma of exactly how to treat a brain AVM and any associated aneurysms. There is considerable uncertainty about which intervention to use when a brain AVM has ruptured at presentation and is amenable to more than one of the available treatments, so we hope that ARUBA will not be the only RCT of interventions for brain AVMs. For now, clinicians can defer to management guidelines that reflect current practice in North America, but are likely to be less representative of practice in other parts of the world. These guidelines have recommended an approach according to the Spetzler-Martin grade of the brain AVM, and the main recommendations are:^{20, 30}

- Surgical excision should be considered as the primary single treatment for grade I and II brain AVMs.
- Surgery alone is unsuitable for grade IV and V brain AVMs.
- Stereotactic radiotherapy is the preferred single treatment for small (≤ 3 cm diameter) grade I and II brain AVMs if the vascular anatomy is unsuitable for surgery.
- A combined approach to completely eradicate the brain AVM nidus using embolisation (perhaps repeatedly) prior to surgery or stereotactic radiotherapy is the treatment of choice for other suitable grade II–V lesions.
- Palliative embolisation (without complete brain AVM eradication) may be beneficial for intractable epilepsy refractory to best antiepileptic drug treatment, or when a progressive neurological deficit is thought to be due to high flow or venous hypertension.

The authors of these guidelines acknowledge that their recommendations are based on non-randomised evidence.³⁰ Technological advances in the treatment of brain AVMs, leading to risk/benefit ratios that are comparable among the three main interventions for some people, are likely to perpetuate uncertainty in the choice of treatment. The heterogeneity of brain AVMs, the relative infrequency of their outcome events, and the strong beliefs held by some interventionists will provide exciting challenges for trialists. However, the recent International Subarachnoid Aneurysm Trial provides an encouraging example for the RCTs that are needed to address both whether and how to treat a brain AVM.³¹

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Authors' affiliations

R Al-Shahi, C Warlow, Division of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh, UK

Correspondence to: Dr R Al-Shahi, Department of Clinical Neurosciences, University of Edinburgh, Western General Hospital, Edinburgh EH4 2XU, UK; rustam.al-shahi@ed.ac.uk

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